(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2007 (18.01.2007)

PCT

(10) International Publication Number
WO 2007/007042 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *A61P 3/04* (2006.01)
C07D 231/40 (2006.01) *A61P 3/06* (2006.01)
A61K 31/4155 (2006.01)

(21) International Application Number: PCT/GB2006/002472

(22) International Filing Date: 3 June 2006 (03.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0514174.2 9 July 2005 (09.07.2005) GB
0516298.7 9 August 2005 (09.08.2005) GB

(71) Applicant (*for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD only*): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **MCKERRECHER, Darren** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **WARING, Michael, James** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; Astrazeneca Ab, SE-151 85 Södertälje (SE).

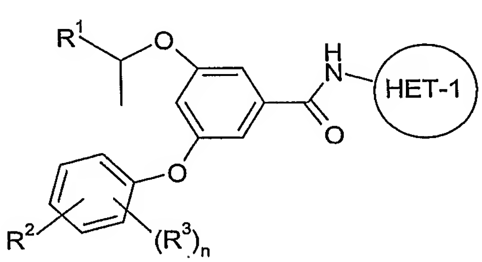
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROARYL BENZAMIDE DERIVATIVES FOR USE AS GLK ACTIVATORS IN THE TREATMENT OF DIABETES



(I)

(57) Abstract: Compounds of formula (I) wherein R^1, R^2, R^3, and HET-1 are as described in the specification, and their salts, are activators of glucokinase (GLK) and are thereby useful in the treatment of, for example, type 2 diabetes. Processes for preparing compounds of formula (I) are also described.

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HETEROARYL BENZAMIDE DERIVATIVES FOR USE AS GLK ACTIVATORS IN THE TREATMENT OF DIABETES

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 6a, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute

treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is dominant in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated extensively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act selectively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

GLK, GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or

synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

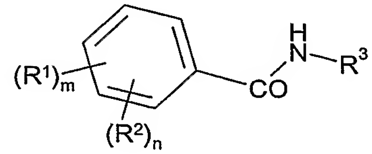
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-cells respectively (32, 33, 34). Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

In WO00/58293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):



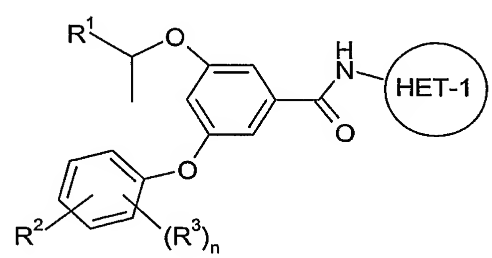
(A)

wherein R^3 is a substituted heterocycle other than a carboxylic acid substituted pyridyl.

International application WO2004/076420 (Banyu) describes compounds which are generally a subset of those described in WO03/015774, wherein for example R^1 is an (substituted) alkyl ether and R^2 is (substituted) phenoxy.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds having a balance of these properties would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK. The compounds of the invention may also have superior potency and/or advantageous physical properties (as described above) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other GLK activators known in the art, as well as those described in WO 03/015774.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is selected from fluoromethoxymethyl, difluoromethoxymethyl and trifluoromethoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring

nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, and/or (for R^6 as a substituent on carbon) halo;

R^7 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, $-S(O)pR^5$ and/or (for R^7 as a substituent on carbon) hydroxy and (1-4C)alkoxy;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced

by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon by 1 substituent selected from hydroxy and R^3 or on an available nitrogen atom by methyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

p is (independently at each occurrence) 0, 1 or 2;

n is 0, 1 or 2;

or a salt thereof.

It will be understood that when R^4 is (1-4C)alkyl substituted with $-C(O)NR^5R^5$, each R^5 is independently selected from hydrogen and (1-4C)alkyl, and therefore this definition of R^4 includes (but is not limited to) (1-4C)alkyl substituted with $-CONH_2$, -CONHMe, $-CONMe_2$ or –CONMeEt.

It will be understood that where a compound of the formula (I) contains more than one HET-2 ring, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^4, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^8, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^3, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

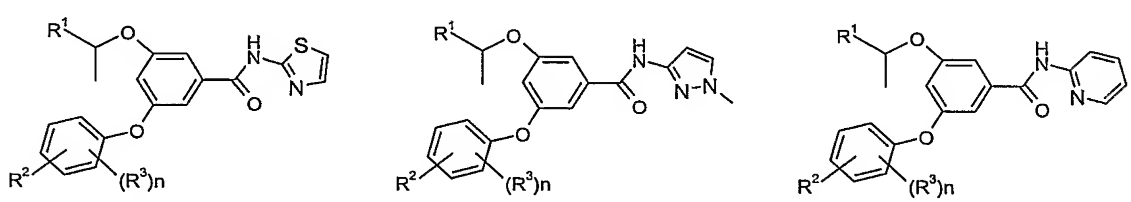
Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically-acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically-acceptable salt.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example,
"(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, the definition of formula (I) encompasses (but is not limited to) the following structures:



Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

It will be understood that HET-2 can be a saturated, or partially or fully unsaturated ring.

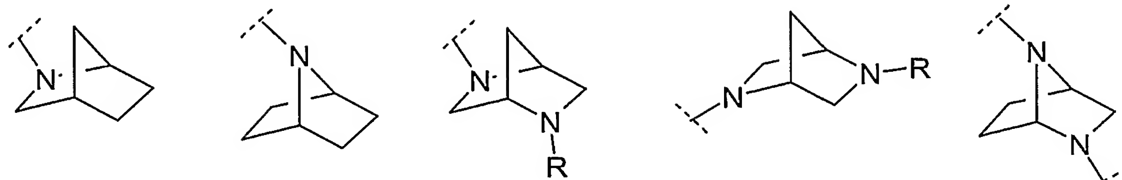
Suitable examples of HET-2 include azetidinyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholino, morpholinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranyl, and 4-pyridonyl.

It will be understood that HET-2 may be linked by any appropriate available C or N atom, therefore for example, for HET-2 as "imidazolyl" includes 1- , 2-, 4- and 5-imidazolyl.

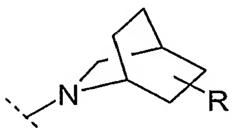
Suitable examples of HET-3 as a 4-6 membered saturated or partially unsaturated heterocyclic ring are morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl.

A suitable example of HET-3 as a 7-membered saturated or partially unsaturated heterocyclic ring is homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl.

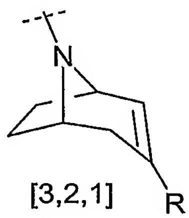
Suitable examples of HET-3 as an 6-10 membered bicyclic heterocyclic ring are bicyclic saturated or partially unsaturated heterocyclyl ring such as those illustrated by the structures shown below (wherein the dotted line indicates the point of attachment to the rest of the molecule and wherein R represents the optional substituents on carbon or nitrogen defined hereinbefore):



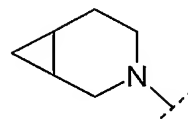
[2,2,1]



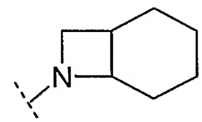
[2,2,2]



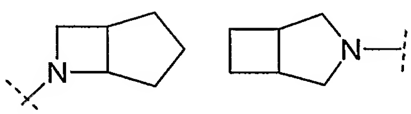
[3,2,1]



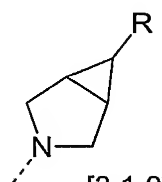
[4,1,0]



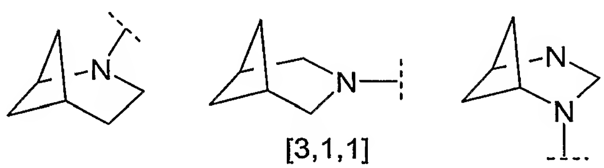
[4,2,0]



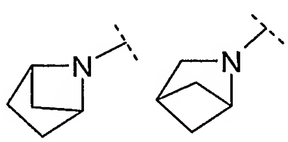
[3,2,0]



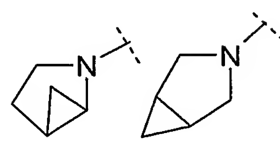
[3,1,0]



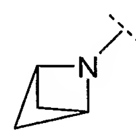
[3,1,1]



[2,1,1]

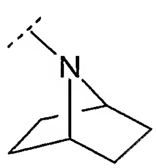


[3,1,0]



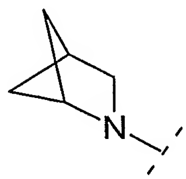
[1,1,1]

In particular HET-3 is a [2,2,1] system such as



(7-azabicyclo[2.2.1]hept-7-yl).

In another embodiment, HET-3 is a [2.1.1] system such as


(2-azabicyclo[2.1.1]hex-2-yl).

It will be appreciated that, where definitions of heterocyclyl groups HET-1 to HET-3 encompass heteroaryl or heterocyclyl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms or unstable structures (such as N-halo compounds). It will be appreciated that the definitions of HET-1 to HET-3 are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1 to HET-3 are not intended to include unstable structures.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy, propoxy, isopropoxy and tertbutoxy; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; examples of **(1-4C)alkylS(O)p(1-4C)alkyl** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-**

4C)alkylamino include dimethylamino, methyl(ethyl)amino, diethylamino, dipropylamino, di-isopropylamino and dibutylamino; examples of **–C(O)(1-4C)alkyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and tert-butylsulfonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

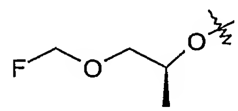
It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

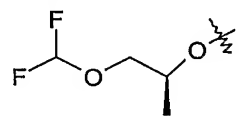
Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter. In particular, each may be used as an individual limitation on the broadest definition of formula (I). Further, each of the following values may be used in combination with one or more of the other following values to limit the broadest defintion of formula (I).

(1) R^1 is fluoromethoxymethyl or difluoromethoxymethyl

(2) R^1 is fluoromethoxymethyl and the configuration is preferably (S), that is the sidechain is:



(3) R^1 is difluoromethoxymethyl and the configuration is preferably (S), that is the sidechain is:



(4) R^2 is $-C(O)NR^4R^5$

(5) R^2 is $-SO_2NR^4R^5$

(6) R^2 is $-S(O)_pR^4$

(7) R^2 is HET-2

(8) R^2 is in the para position relative to the ether linkage

(9) n is 0 or 1

(10) n is 0

(11) n is 1, R^2 is in the para position relative to the ether linkage, R^3 is in the ortho position relative to the ether linkage

(12) n is 1, R^2 is in the para position relative to the ether linkage, R^3 is in the meta position relative to the ether linkage

(13) n is 1

(14) n is 2

(15) n is 2 and both R^3 are halo

(16) n is 2 and each R^3 is independently fluoro or chloro

(17) n is 2, R^2 is in the para position relative to the ether linkage and each R^3 is in an ortho position relative to the ether linkage

(18) n is 2, both R^3 are halo, R^2 is in the para position relative to the ether linkage and each R^3 is in an ortho position relative to the ether linkage

(19) n is 2, both R^3 are halo, R^2 is in the para position relative to the ether linkage and one R^3 is in an ortho position relative to the ether linkage and the other R^3 is in a meta position relative to the ether linkage

(20) R^3 is chloro or fluoro

(21) R^3 is fluoro

(22) R^3 is chloro

(24) n is 2 and both R^3 are fluoro

(25) n is 2 and one R^3 is fluoro and the other is chloro

(26) p is 0

(27) p is 1

(28) p is 2

(29) HET-1 is a 5-membered heteroaryl ring

(30) HET-1 is a 6-membered heteroaryl ring

(31) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(32) HET-1 is substituted with 1 substituent selected from R^6

(33) HET-1 is unsubstituted

(34) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(35) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(36) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(37) HET-1 is pyrazolyl, for example N-methylpyrazolyl

(38) HET-1 is pyridyl or pyrazinyl

(39) HET-1 is pyrazinyl

(40) HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl

(41) HET-1 is pyrazolyl (optionally substituted with ethyl, isopropyl or 1 or 2 methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl (optionally substituted with methyl) and thiadiazolyl (optionally substituted with methyl)

(42) HET-1 is pyrazolyl (optionally substituted with ethyl, isopropyl, difluoromethyl, or 1 or 2 methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally

substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl (optionally substituted with methyl) and thiadiazolyl (optionally substituted with methyl)

(43) HET-1 is selected from pyrazinyl (optionally substituted with methyl), pyrazolyl (optionally substituted on carbon by methyl), methylthiadiazolyl (particularly 1,2,4-thiadiazol-5-yl, more particularly 3-methyl-1,2,4-thiadiazol-5-yl), thiazolyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro) and isoxazolyl

(44) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl

(45) R^6 is selected from methyl, ethyl, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(46) R^6 is selected from methyl, ethyl, chloro, fluoro, hydroxymethyl and methoxymethyl

(47) R^6 is selected from methyl or ethyl

(48) R^6 is methyl

(49) R^6 is selected from (1-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl

(50) R^6 is selected from methyl, ethyl, isopropyl and methoxymethyl

(51) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro; preferably both are methyl and at least one is on an available nitrogen atom

(52) R^4 is hydrogen

(53) R^4 is (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$]

(54) R^4 is (1-4C)alkyl [substituted by 1 substituent selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$]

(55) R^4 is (1-4C)alkyl

(56) R^4 is (1-4C)alkyl substituted by $-OR^5$

(57) R^4 is (1-4C)alkyl substituted by HET-2

(58) R^4 is (3-6C)cycloalkyl, particularly cyclopropyl or cyclobutyl

(59) R^4 is (3-6C)cycloalkyl substituted by a group selected from R^7

(60) R^4 is (3-6C)cycloalkyl substituted by a group selected from $-OR^5$ and (1-4C)alkyl

(61) R^4 is selected from (1-4C)alkyl and (3-6C)cycloalkyl

(62) R^4 is selected from methyl, ethyl, cyclopropyl and cyclobutyl

(63) R^4 is HET-2

(64) R^4 is selected from hydrogen, (1-4C)alkyl, and (1-4C)alkyl substituted with $-OR^5$

(65) HET-2 is unsubstituted

(66) HET-2 is substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(67) HET-2 is a fully saturated ring system

(68) HET-2 is a fully unsaturated ring system

(69) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl

(70) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl

(71) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl

(72) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(73) HET-2 is selected from morpholino, furyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(74) HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(75) HET-2 is oxadiazolyl or pyrazolyl

(76) R^5 is hydrogen

(77) R^5 is (1-4)alkyl, preferably methyl

(78) R^5 is hydrogen or methyl

(79) R^7 is a substituent on carbon and is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, -C(O)(1-4C)alkyl, -C(O)NR^{4}R^5, (1-4C)alkoxy(1-4C)alkyl, and hydroxy(1-4C)alkyl

(80) R^7 is a substituent on carbon and is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, -C(O)(1-4C)alkyl, -C(O)NR^{4}R^5, and hydroxy(1-4C)alkyl

(81) R^7 is a substituent on carbon and is selected from hydroxy, methoxy, -COMe, -CONH$_2$, -CONHMe, -CONMe$_2$, and hydroxymethyl

(82) R^7 is a substituent on carbon and is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(83) R^7 is a substituent on carbon and is selected from methyl, ethyl, methoxy and hydroxy

(84) R^7 is a substituent on nitrogen and is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, -C(O)NR^{4}R^5, (1-4C)alkoxy(1-4C)alkyl, and hydroxy(1-4C)alkyl

(85) R^7 is a substituent on nitrogen and is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(86) R^7 is methyl

(87) R^8 is selected from methyl, hydroxy, methoxy, -CONH$_2$, -CONHMe, -CONMe$_2$, hydroxymethyl, hydroxyethyl, -NHMe and –NMe$_2$(88) R^8 is is selected from methyl, -CONH$_2$, hydroxyethyl and hydroxy

(89) R^8 is selected from (1-4C)alkyl and (1-4C)alkoxy

(90) R^8 is selected from methyl, methoxy and isopropoxy

(91) R^8 is methyl

(92) R^9 is selected from methyl, hydroxy, methoxy, -CONH$_2$, -CONHMe, -CONMe$_2$, hydroxymethyl, hydroxyethyl, -NHMe and –NMe$_2$(93) R^9 is methyl

(94) HET-3 is a fully saturated ring

(95) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(96) R^4 and R^5 together with the nitrogen to which they are attached form a ring as defined by HET-3

(97) HET-3 is selected from pyrrolidinyl and azetidinyl

(98) HET-3 is azetidinyl

(99) HET-3 is a 4 to 6-membered saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(100) HET-3 is a 7-membered saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(101) HET-3 is an 6 to 10-membered bicyclic saturated or partially unsaturated heterocyclic ring as hereinbefore defined

(102) HET-3 is 7-azabicyclo[2.2.1]hept-7-yl or 2-azabicyclo[2.1.1]hex-2-yl

(103) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(104) HET-3 is unsubstituted

(105) HET-3 is substituted by methyl, methoxy or isopropoxy

(106) R^2 is $-C(O)NR^4R^5$ or $-SO_2NR^4R^5$

(107) R^2 is azetidinylcarbonyl or azetidinylsulfonyl

(108)) R^2 is azetidinylcarbonyl or methylsulfonyl

(109) R^2 is azetidinylcarbonyl, azetidinylsulfonyl or (1-4C)alkylsulfonyl

(110) R^2 is azetidinylcarbonyl, azetidinylsulfonyl or methylsulfonyl

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In one aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$ and $-S(O)_pR^4$;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

R^3 is selected from halo;

R^4 is selected from hydrogen and (1-4C)alkyl;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl, and/or (for R^6 as a substituent on carbon) halo;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

R^3 is halo;

R^4 is selected from hydrogen and (1-4C)alkyl;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl, and/or (for R^6 as a substituent on carbon) halo;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2

substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

R^3 is halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl, and/or (for R^6 as a substituent on carbon) halo;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl; wherein R^1 is optionally substituted with methyl or ethyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, wherein R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl, piperidinyl, morpholino or an (optionally N-substituted) piperazino ring;

R^3 is chloro or fluoro;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is difluoromethoxymethyl;

HET-1 is N-methylpyrazolyl;

R^2 is $-CONR^4R^5$ wherein R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl ring;

R^3 is chloro;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl; wherein HET-1 is optionally substituted with methyl or ethyl;

R^2 is$-SO_2R^4$, wherein R^4 is (1-4C)alkyl;

R^3 is chloro or fluoro;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl; wherein HET-1 is optionally substituted with methyl or ethyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, wherein R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl, piperidinyl, morpholino or an (optionally N-substituted) piperazino ring; or

R^2 is$-SO_2R^4$, wherein R^4 is (1-4C)alkyl;

R^3 is chloro or fluoro;

n is 0 or 1.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from fluoromethoxymethyl and difluoromethoxymethyl;

HET-1 is N-methylpyrazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, wherein R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl, piperidinyl, morpholino or an (optionally N-substituted) piperazino ring; or

R^2 is$-SO_2R^4$, wherein R^4 is (1-4C)alkyl;

R^3 is chloro or fluoro;

n is 0 or 1.

Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

Particular compounds of the invention include any one or more of:

3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and

3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or

3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-{[4-(methylsulfonyl)phenyl]oxy}benzamide;

or a salt thereof.

The compounds of the invention may be administered in the form of a pro-drug.

A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and

carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. It will be understood that an acid addition salt may be formed with any sufficiently basic group which may for example be in HET-1 or may for example be a substituent R^2. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided the a compound of Formula (I) as defined above or a pharmaceutically-acceptable salt thereof for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula (I), or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

Further according to the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount

of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the combined treatment or prevention, particularly treatment, of diabetes and obesity.

According to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

According to another aspect of the invention there is provided a compound of Formula (I) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment or prevention, particularly treatment of obesity.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Compounds of the invention may be particularly suitable for use as pharmaceuticals, for example because of favourable physical and/or pharmacokinetic properties and/or toxicity profile.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration

by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). Dosage forms suitable for oral use are preferred.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol

monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents,

which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the

range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;

2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);

3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, and GLP-1 agonists);

4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;

5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);

6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

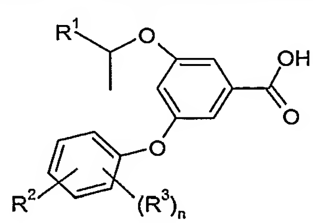
14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts thereof.

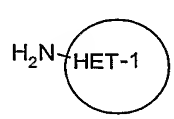
A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), which comprises a process a) to e) (wherein the variables are as defined hereinbefore for compounds of Formula (I) unless otherwise defined):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as defined for formula (I) or is a precursor thereof;



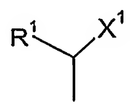
(III)



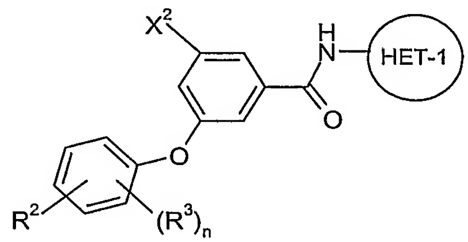
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),

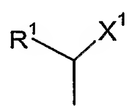


(V)

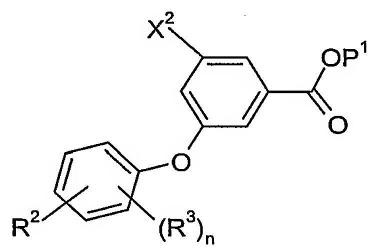


(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as defined for formula (I) or is a precursor thereof; process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



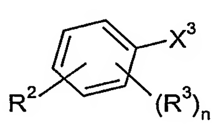
(V)



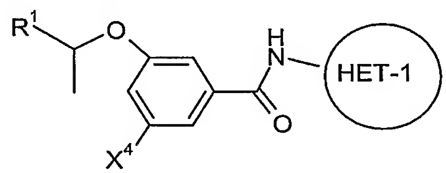
(VII)

or

(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



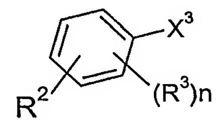
(VIII)



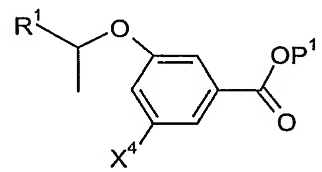
(IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as defined for formula (I) or is a precursor thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



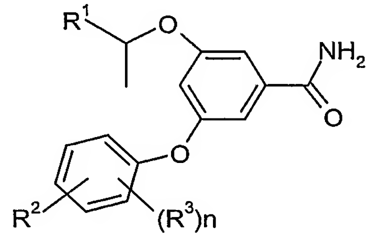
(VIII)



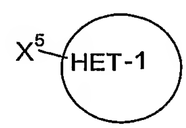
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



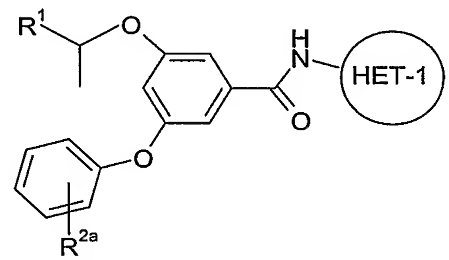
(XI)



(XII);

wherein X^5 is a leaving group; and wherein R^1 is as defined for formula (I) or is a precursor thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2 as $-CONR^4R^5$ or $-SO_2R^4R^5$, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) converting a precursor of R^1 into R^1;

iii) removing any protecting groups; and/or

iv) forming a salt thereof.

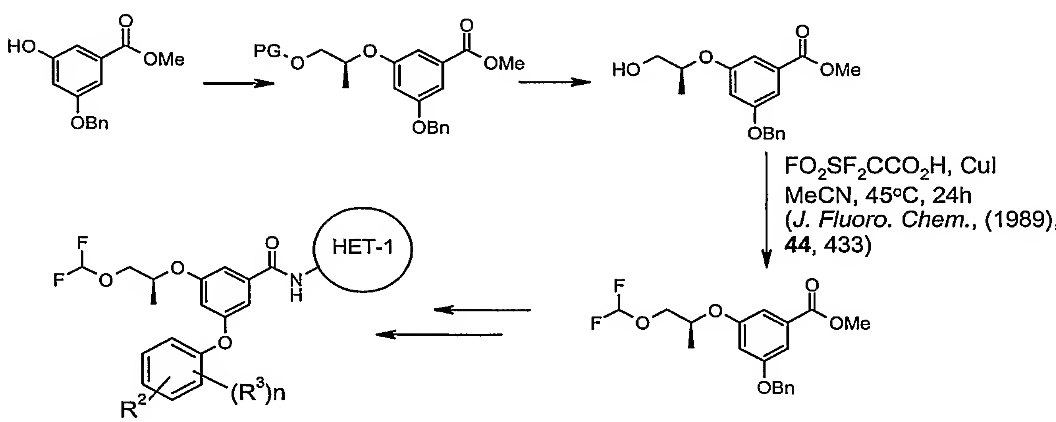
Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy, methanesulfonyloxy, or p-toluenesulfonyloxy; or a group (such as a hydroxy group) that may be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

Suitable precursors to R^1 include a hydroxy group or a protected hydroxy group, such as any suitable protected hydroxy group known in the art, for example simple ethers such as a methyl ether, or silylethers such as –OSi[(1-4C)alkyl]$_3$ (wherein each (1-4C)alkyl group is independently selected from methyl, ethyl, propyl, isopropyl, and tertbutyl). Examples of such trialkylsilyl groups are trimethylsilyl, triethylsilyl, triisopropylsilyl and tert-butyldimethylsilyl. Further suitable silyl ethers are those containing phenyl and substituted phenyl groups, such as –Si(PhMe$_2$) and –Si(TolMe$_2$) (wherein Tol = methylbenzene). Further suitable values for hydroxy protecting groups are given hereinafter. R^1 itself may then be generated by removing the hydroxy protecting group if present, and then by reacting with, for example 2-(fluorosulphonyl)difluoroacetic acid in the presence of copper (I)iodide to give the compound wherein R^1 is difluoromethoxymethyl. This reaction is illustrated in Scheme 1. Other values of R^1 may be generated similarly or by methods well known in the art, see for example Bull. Chem. Soc. Japan, 73 (2000), 471-484, 471-484, International Patent application WO 2002/050003 and Bioorganic and Medicinal Chemistry Letters, (2001), *11*, 407.

Compounds of Formulae (III) to (XII) are commercially available, or are known in the art, or may be made by processes known in the art, for example as shown in the accompanying Examples. For further information on processes for making such compounds, we refer to our PCT publications WO 03/000267, WO 03/015774, WO 03/000262, WO 2004/076420, WO 2005/054200, WO 2005/054233, WO 2005/044801 and WO 2005/056530 and references therein. In general it will be appreciated that any aryl-O or alkyl-O bond may be formed by nucleophilic substitution or metal catalysed processes, optionally in the presence of a suitable base.

Compounds of Formula (XIII) may be made by processes such as those shown in processes a) to d) and/or by those processes mentioned above for compounds of formulae (III) to (XII).

Compounds of formulae (III), (IX), (X), (XI) and (XIII) may be made by reaction of suitable precursors with compounds of formula (V) or derivatives thereof, depending on the nature of the R^1 group or its precursor, for example, by nucleophilic displacement of a leaving group X^1 in a compound of formula (V). Compounds of formula (V) are generally commercially available or may be made by simple functional group interconversions from comercially available compounds, or by literature methods. Where the compound of formula (V) contains a precursor to R^1, the R^1 group may be generated in the compound of formula (III), (IX), (X), (XI) or (XIII) as appropriate using reactions such as those illustrated in Scheme 1 below. An illustrative example is shown in the scheme below, and/or in the accompanying examples.



[PG is protecting group].

Scheme 1

Examples of conversions of a compound of Formula (I) into another compound of Formula (I) well known to those skilled in the art, include functional group interconversions such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions. An example would be removal of an R^3=chloro substituent, for example by reaction with hydrogen at atmospheric or elevated pressure, in a suitable solvent such as THF/methanol or ethanol.

It will be understood that substituents R^2, R^3 and/or R^6 may be introduced into the molecule at any convenient point in the synthetic sequence or may be present in the starting materials. A precursor to one of these substituents may be present in the molecule during the process steps a) to e) above, and then be transformed into the desired substituent as a final step to form the compound of formula (I); followed where necessary by

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) converting a precursor of R^1 into R^1;

iii) removing any protecting groups; and/or

iv) forming a salt thereof.

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably (1-4C)alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in the presence of dimethylaminopyridine (DMAP) in a suitable solvent such as dichloromethane (DCM), chloroform or dimethylformamide (DMF) at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as DCM. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and 80°C.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or tetrahydrofuran (THF), with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate; process b) could also be carried out using a precursor to the ester

of formula (VII) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; process c) could also be carried out using a precursor to the ester of formula (X) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 200°C, optionally using microwave heating or metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process e) - coupling reactions of amino groups with carboxylic or sulfonic acids or acid derivatives to form an amide are well known in the art and are described above for Process a).

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (III), (IX) and/or (XI) wherein R^1 is as defined herein, are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (XIII) are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific

examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include methyl, t-butyl, lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); tetrahydropyran-2-yl; aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, nucleophilic displacement, acid-, base, metal- or enzymically-catalysed hydrolysis, catalytic hydrogenolysis/hydrogenation or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups. For example, methylether protecting groups for hydroxy groups may be removed by trimethylsilyliodide. A tert-butyl ether protecting group for a hydroxy group may be removed by hydrolysis, for example by use of hydrochloric acid in methanol.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred aspects and embodiments of the compounds of the invention described herein also apply.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) with a field strength (for proton) of 300MHz (generally using a Varian Gemini 2000) or 400 MHz (generally using a Bruker Avance DPX400), unless otherwise stated, and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) Purification by chromatography generally refers to flash column chromatography, on silica unless otherwise stated. Column chromatography was generally carried out using prepacked silica cartridges (from 4g up to 400g) such as Redisep™ (available, for example, from Presearch Ltd, Hitchin, Herts, UK) or Biotage (Biotage UK Ltd, Hertford, Herts, UK), eluted using a pump and fraction collector system;

(vii) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phemonenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ spectrometer. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and

values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

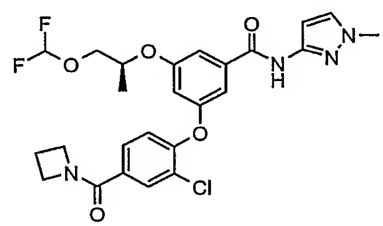
(viii) Suitable microwave reactors include "Smith Creator", "CEM Explorer", "Biotage Initiator sixty" and "Biotage Initiator eight".

<u>Abbreviations</u>

DCM	dichloromethane;
DEAD	diethylazodicarboxylate;
DIAD	diisopropylazodicarboxylate;
DIPEA	*N,N*-Diisopropylethylamine;
DMA	dimethylacetamide
DMSO	dimethyl sulphoxide;
DMF	dimethylformamide;
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate
HPLC	high pressure liquid chromatography
HPMC	Hydroxypropylmethylcellulose;
LCMS	liquid chromatography / mass spectroscopy;
NMP	*N*-methyl-2-pyrrolidone;
NMR	nuclear magnetic resonance spectroscopy;
RT	room temperature;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid;
$CDCl_3$	deuterochloroform.

All compound names were derived using ACD NAME computer package.

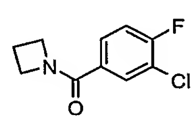
Example 1: 3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (70 mg, 0.21 mmol), 1-(3-chloro-4-fluorobenzoyl)azetidine (44 mg, 0.21 mmol) and potassium carbonate (57 mg, 0.41 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The mixture was washed with water (20 mL), brine (50 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (35 mg).

^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 2.40 (quintet, 2H), 3.82 (s, 3H), 3.98 (m, 2H), 4.20-4.45 (m, 4H), 4.57 (m, 1H), 6.10-6.45 (t, 1H), 6.78 (d, 2H), 7.04 (m, 1H), 7.22 (s, 1H), 7.28 (m, 2H), 7.54 (d, 1H), 7.81 (s, 1H), 8.50 (s, 1H). *m/z* 535 $(M+H)^+$

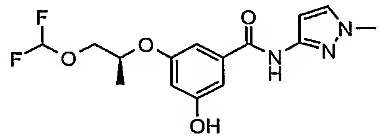
1-(3-Chloro-4-fluorobenzoyl)azetidine



To a solution of 3-chloro-4-fluorobenzoic acid (1.74 g, 10.0 mmol) in DCM (50 mL) was added oxalyl chloride (1.05 mL, 12.0 mmol) and DMF (1 drop). The mixture was stirred at ambient temperature for 16 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride and azetidine hydrochloride (1.12 g, 12 mmol) were taken up in DCM (25 mL) and triethylamine (4.18 mL, 30 mmol) added to the mixture, which was stirred at ambient temperature for 2 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium

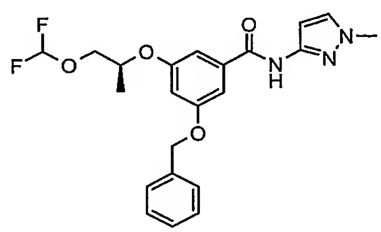
hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate / isohexane to give the title compound (1.64 g).
^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H).

3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (0.1 g, 0.23 mmol) was dissolved in ethanol (3 mL) and THF (3 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (0.01 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at RT for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off through celite and the filtrate concentrated *in vacuo* to give the desired compound (70 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 3.71 (s, 3H), 3.80-3.95 (m, 2H), 4.51 (sextet, 1H), 5.96-6.36 (t, 1H), 6.53 (s, 1H), 6.73 (s, 1H), 6.91 (s, 1H), 6.96 (s, 1H), 7.22 (s, 1H), 8.83 (s, 1H). *m/z* 342 $(M+H)^+$.

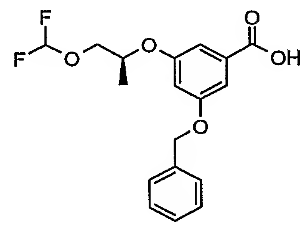
3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



DIPEA (0.198 mL, 1.14 mmol) was added to a mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid (0.1 g, 0.28 mmol), 3-amino-1-methyl pyrazole (39 mg, 0.4 mmol) and HATU (0.227 g, 0.6 mmol) in DMF (3 mL) and stirred at RT for 20 hours. Ethyl acetate (30 mL) was added and the

mixture washed with water (30 mL), brine (30 mL), dried (MgSO4), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound (0.1 g). ^{1}H NMR δ ($CDCl_3$): 1.36 (d, 3H), 3.68 (s, 3H), 3.82-3.95 (m, 2H), 4.48 (sex, 1H), 5.00 (s, 2H), 6.19 (t, 1H), 6.63 (s, 1H), 6.73 (s, 1H), 6.93 (s, 1H), 7.03 (s, 1H), 7.28 (m, 1H), 7.35 (m, 5H), 8.59 (s, 1H). *m/z* 432 $(M+H)^+$.

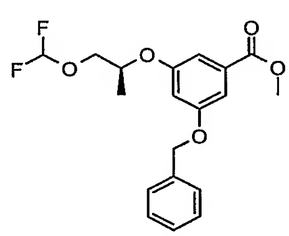
<u>3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid</u>



Lithium hydroxide monohydrate (19 mg, 0.45 mmol) in water (2 mL) was added to methyl 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoate (0.11 g, 0.3 mmol) in THF (4 mL) and the mixture stirred at RT for 20 hours. The THF was removed *in vacuo* and the aqueous layer adjusted to pH3 with citric acid then extracted into ethyl actetate (2 x 30 mL). The organics were washed with water (30 mL), brine (30 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give the desired compound (0.1 g).

^{1}H NMR δ (d_6-DMSO): 1.27 (d, 3H), 4.00 (m, 2H), 4.75 (sextet, 1H), 5.15 (s, 2H), 6.72 (t, 1H), 7.08 (t, 1H), 7.16 (t, 1H), 7.41 (m, 5H), 12.95 (s, 1H). *m/z* 351 $(M+H)^+$.

<u>Methyl 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoate</u>

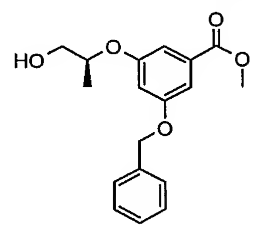


2-(Fluorosulphonyl)difluoroacetic acid (0.239 mL, 2.31 mmol) was added dropwise, with stirring, to a degassed mixture of methyl 3-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-5-

[(phenylmethyl)oxy]benzoate (0.73 g, 2.31 mmol) and copper (I) iodide (88 mg, 0.46 mmol) in acetonitrile (10 mL) at 45°C. The reaction was stirred at 45°C for 24 hours. The solvent was removed *in vacuo* and ethyl acetate (30 mL) added. The organics were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-30% ethyl acetate in isohexane, to give the desired compound (0.11 g).

^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 3.93 (s, 3H), 4.00 (m, 2H), 4.63 (sextet, 1H), 5.10 (s, 2H), 6.28 (t, 1H), 6.77 (t, 1H), 7.28 (t, 1H), 7.41 (m, 6H). *m/z* 367 $(M+H)^+$.

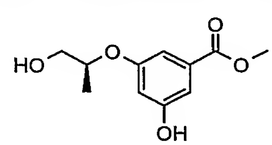
<u>Methyl 3-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-5-[(phenylmethyl)oxy]benzoate</u>



Benzyl bromide (1.89 g, 7.20 mmol) was added to a mixture of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate (1.55 g, 6.86 mmol) and potassium carbonate (1.89 g, 0.014 mol) in DMF (16 mL) and the reaction stirred at RT for 20 hours. Ethyl acetate (40 mL) was added and the mixture washed with water (40 mL), saturated sodiumbicarbonate solution (40 mL), brine (40 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give a red oil which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound (1.7 g).

^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 1.95 (m, 1H), 3.76 (m, 2H), 3.92 (s, 3H), 4.53 (m, 1H), 5.11 (s, 2H), 6.78 (t, 1H), 7.25 (m, 1H), 7.32 (m, 1H), 7.45 (m, 5H). *m/z* 317 $(M+H)^+$.

<u>Methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate</u>

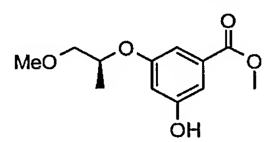


Trimethylsilyl iodide (115 mL, 0.79mol) was added to a solution of methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate (38.01 g, 0.158mol) in acetonitrile (500 mL) and stirred for 24 hours. Methanol (300 mL) was added and the reaction stirred for 10

mins. 10% w/v Aqueous sodium thiosulfate pentahydrate (100 mL) was added to the mixture and stirred for 20 mins. The reaction mixture was neutralised with saturated aqueous sodium bicarbonate solution, the organic solvents removed *in vacuo*, and the product extracted into ethyl acetate (4 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The crude material was crystallised from ethyl acetate to give the title compound (16.80 g)

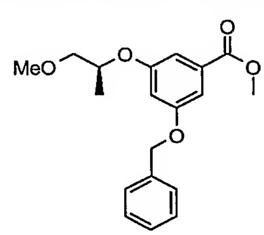
^{1}H NMR δ (d_6-DMSO): 1.18 (d, 3H), 3.40-3.55 (m, 2H), 3.80 (s, 3H), 4.35 (sex, 1H), 4.80 (t, 1H), 6.57 (m, 1H), 6.90 (m, 2H), 9.75 (s, 1H); *m/z* 225 $(M-H)^-$.

Methyl 3-Hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate



Methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoate (50.0 g, 0.152 mmol) was dissolved in a mixture of THF:ethanol (600 mL) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (5.0 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, and the filtrate concentrated *in vacuo* to give the desired compound (36.7 g). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.55 (m, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 9.8 (s, 1H).

Methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoate

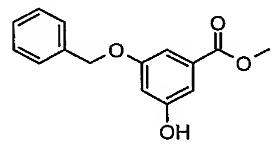


To a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (77.4 mmol) in THF was added polymer-supported triphenylphosphine (51.7g of 3 mmol/g loading, 155 mmol) and (*R*)-(-)-1-methoxy-2-propanol (102 mmol). The stirred solution was blanketed with

argon and cooled in an ice bath. A solution of DIAD (116 mmol) was added dropwise by syringe over 10 minutes. The solution was stirred for 20 minutes and filtered, washing the residue with THF (500 mL). The filtrate and washings were combined, and evaporated to give the desired compound which was used without further purification.

^{1}H NMR δ (d_6-DMSO): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H). The ^{1}H NMR spectrum also contained signals consistent with a small amount of bis(1-methylethyl)hydrazine-1,2-dicarboxylate.

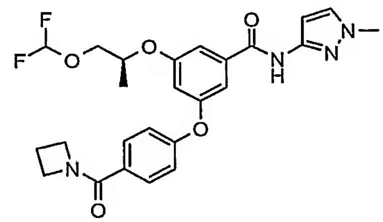
Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) was added potassium carbonate (9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with DCM (1 x 3 L and 2 x 5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was evaporated in *vacuo*, and the crude product chromatographed in 3 batches (flash column, 3 x 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The crude eluant was further chromatographed in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to give the desired compound (21% yield);

^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H).

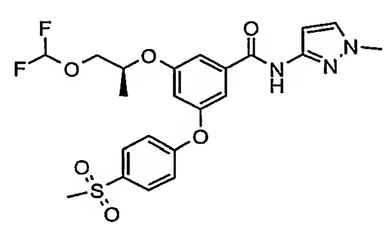
Example 2: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (35 mg, 0.07 mmol) and triethylamine (0.028 mL, 0.2 mmol) was dissolved in ethanol (3 mL) and THF (3 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (4 mg) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at RT for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off through celite and the filtrate concentrated *in vacuo* to give a colourless oil which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the desired compound (19 mg). ^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 2.30 (quin, 2H), 3.72 (s, 3H), 3.80 (m, 2H), 4.10-4.35 (m, 4H), 4.57 (m, 1H), 6.00-6.38 (t, 1H), 6.70 (m, 2H), 6.96 (d, 2H),7.01 (m, 1H), 7.17 (m, 1H), 7.21 (m, 1H), 7.58 (d, 2H), 8.23 (s, 1H). *m/z* 501 $(M+H)^+$.

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described in **Example 1.**

Example 3: 3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-{[4-(methylsulfonyl)phenyl]oxy}benzamide



A mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (220 mg, 0.64 mmol), 4-fluorophenyl methyl sulfone (113 mg, 0.64 mmol) and potassium carbonate (178 mg, 1.29 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 4 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The organics were washed with water (20 mL), brine (50 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give a yellow oil. The residue was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (174 mg).

^{1}H NMR δ ($CDCl_3$): 1.38 (d, 3H), 3.10 (s, 3H), 3.77 (s, 3H), 4.00 (m, 2H), 4.64 (m, 1H), 6.28 (t, 1H), 6.82 (m, 2H), 7.15 (m, 3H), 7.31 (m, 2H), 7.94 (d, 2H), 8.92 (s, 1H); *m/z* 496 $(M+H)^+$

The preparation of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described in **Example 1**.

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity

Enzymatic activity of recombinant human pancreatic GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the linear increase with time of optical density at 340nm (Matschinsky et al 1993). Activation of GLK by compounds can be assessed using this assay in the presence or absence of GLKRP as described in Brocklehurst et al (Diabetes 2004, **53**, 535-541).

Production of recombinant GLK and GLKRP:

Human GLK and GLKRP cDNA was obtained by PCR from human pancreatic and hepatic mRNA respectively, using established techniques described in Sambrook J, Fritsch EF & Maniatis T, 1989. PCR primers were designed according to the GLK and GLKRP

cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 mL cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1mL 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40mL of cells were incubated with 1mL of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/mL or ampicillin at 100mg/mL.

Expression

GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the

FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

(2) Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent reduction in glucose excursion was determined using the AUC in the vehicle-control group as zero percent reduction.

Compounds of the invention generally activate glucokinase with an EC_{50} of less than about 500nM. For example, Example 1 has an EC_{50} of 40nM.

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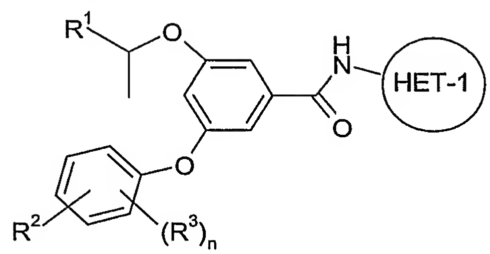
Claims:

1. A compound of Formula (I):



(I)

wherein:

R^1 is selected from fluoromethoxymethyl, difluoromethoxymethyl and trifluoromethoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$], (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, and/or (for R^6 as a substituent on carbon) halo;

R^7 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, -C(O)NR^{4}R^5, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, –S(O)pR^5 and/or (for R^7 as a substituent on carbon) hydroxy and (1-4C)alkoxy;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a -CH_2- group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a -CH_2- group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon by 1 or 2 substituents independently selected from R^8; and/or substituted on an available nitrogen atom by a substituent selected from R^9; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a -CH_2- group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon by 1 substituent selected from hydroxy and R^3 or on an available nitrogen atom by methyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, -C(O)NR^{4}R^5, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)pR^5;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, -C(O)NR^{4}R^5, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)pR^5;

p is (independently at each occurrence) 0, 1 or 2;

n is 0, 1 or 2;
or a salt thereof.

2. A compound of the formula (I) as claimed in Claim 1 or a salt thereof wherein R^1 is fluoromethoxymethyl or difluoromethoxymethyl.

3. A compound of the formula (I) as claimed in Claim 1 or Claim 2 or a salt thereof wherein R^1 has the (S) configuration.

4. A compound of the formula (I) as claimed in Claim 1, Claim 2, or Claim 3 or a salt thereof, wherein HET-1 is a 5-membered ring.

5. A compound of the formula (I) as claimed in any one of Claims 1 to 4 or a salt thereof, wherein R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$ and R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclyl ring system as defined by HET-3.

6. A compound of the formula (I) as claimed in any one of Claims 1 to 5, or a salt thereof, wherein HET-3 is a 4- to 6-membered ring.

7. A compound of the formula (I) as claimed in any one of Claims 1 to 5, or a salt thereof, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form an azetidinyl ring.

8. A compound of the formula (I) as claimed in any one of Claims 1 to 4 wherein R^2 is selected from azetidinylcarbonyl, azetidinylsulfonyl and (1-4C)alkylsulfonyl.

9. A compound of the formula (I) as claimed in Claim 1, which is any one or more of the following:
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-{[4-(methylsulfonyl)phenyl]oxy}benzamide;
or a salt thereof.

10. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

11. A compound according to any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof for use as a medicament.

12. The use of a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt thereof for the preparation of a medicament for treatment of a disease mediated through GLK.

13. The use of a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt thereof for the preparation of a medicament for treatment of type 2 diabetes.

14. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

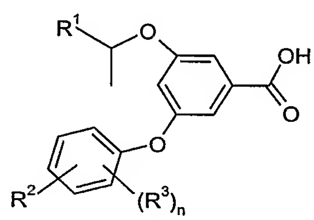
15. The method of Claim 14 wherein the GLK mediated disease is type 2 diabetes.

16. A compound according to any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof for use as a medicament for the treatment of a disease mediated through GLK.

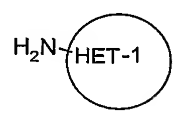
17. A compound according to claim 16 wherein the disease mediated through GLK is type-2 diabetes.

18. A process for the preparation of a compound of Formula (I) as claimed in any one of Claims 1 to 9, which comprises a process a) to e) (wherein the variables are as defined for compounds of Formula (I) in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as defined for formula (I) or is a precursor thereof;



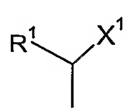
(III)



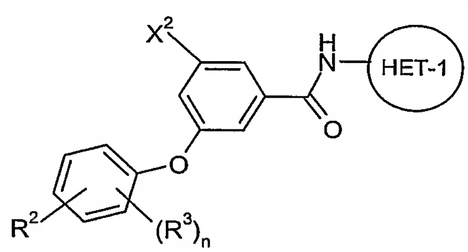
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),

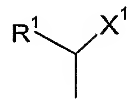


(V)

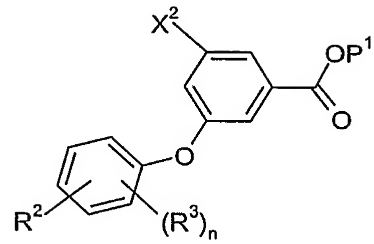


(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as defined for formula (I) or is a precursor thereof; process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group, followed by ester hydrolysis and amide formation;



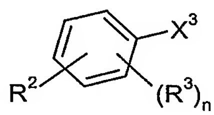
(V)



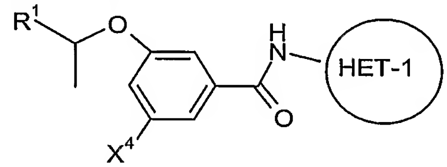
(VII)

or

(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



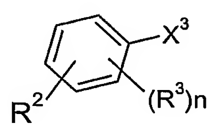
(VIII)



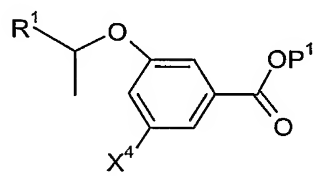
(IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as defined for formula (I) or is a precursor thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation;



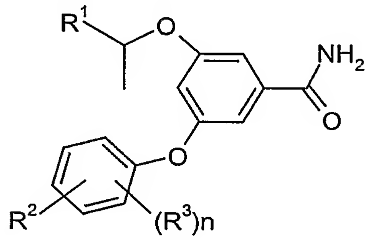
(VIII)



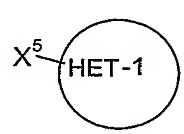
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



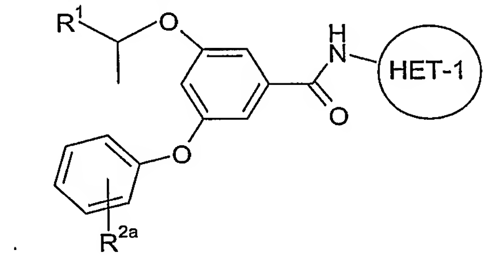
(XI)



(XII);

wherein X^5 is a leaving group; and wherein R^1 is as defined for formula (I) or is a precursor thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2 as $-CONR^4R^5$ or $-SO_2R^4R^5$, such as a carboxylic acid, ester or anhydride (for $R^2 = -CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) converting a precursor of R^1 into R^1;

iii) removing any protecting groups; and/or

iv) forming a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/002472

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D231/40 A61K31/4155 A61P3/04 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/015774 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; BOYD, SCOTT; CAULKETT, PETER,) 27 February 2003 (2003-02-27) cited in the application page 22, line 8 - line 17	1-18

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2006	31/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Johnson, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/002472

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14, 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/002472

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